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Global stability for an HIV-1 infection model including an eclipse stage of infected cells

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ABSTRACT

We consider the mathematical model for the viral dynamics of HIV-1 introduced in Rong et al. (2007) [37]. One main feature of this model is that an eclipse stage for the infected cells is included and cells in this stage may revert to the uninfected class. The viral dynamics is described by four nonlinear ordinary differential equations. In Rong et al. (2007) [37], the stability of the infected equilibrium has been analyzed locally. Here, we perform the global stability analysis using two techniques, the Lyapunov direct method and the geometric approach to stability, based on the higher-order generalization of Bendixson's criterion. We obtain sufficient conditions written in terms of the system parameters. Numerical simulations are also provided to give a more complete representation of the system dynamics.

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1. Introduction

In the last decade, the mathematical models for the viral dynamics of HIV-1 have proved to be useful for describing the interaction between virus and host cells in individual patients [35].

In recent years, much work has been done on the viral dynamics of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections. These studies have provided insights on viral replication, host cell death rate and treatment efficacy [36].

In the basic mathematical modelling of viral dynamics, used often to describe the dynamics of infections by HIV, HBV and HCV, a simplified view of viral infection is assumed, through the coupled evolution of three populations: uninfected cells, productively infected cells, and free viral particles. The viral dynamics is therefore described by the time evolution of three variables that represent the concentrations of the three populations, [33].

In 2007, Rong and coworkers, [37], studied an extension of the basic model of HIV-1 infection. One main feature of their model is that an eclipse stage for the infected cells is included and a portion of these cells is reverted to the uninfected class. From the mathematical point of view, their extension implies that an extra cell population must be considered, resulting in a four-dimensional model of nonlinear ordinary differential equations (we remark that ordinary differential equations models are only one of the ways to describe the eclipse stage. Age-structured models have also been developed to address this, see e.g. [1,32,38]).

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In [37], the stability of the infected equilibrium has been analyzed locally. Nevertheless, the question of global stability for this type of viral infections dynamics is an intriguing and a difficult task. In fact, the four-dimensional nature of the model makes the use of nonlinear stability methods nontrivial.

For this main reason, we reconsider the problem set in [37] and deal with the issue of global stability. More precisely, we study the conditions of global stability for the equilibrium states employing two distinct techniques: Lyapunov's direct method and the Li and Muldowney's geometric approach to global stability.

The well-known Lyapunov direct method is undoubtedly one of the most powerful tools for nonlinear stability analysis, [27]. The main advantage of Lyapunov direct method is that it is directly applicable to nonlinear systems. However, the method requires an auxiliary function, the Lyapunov function, which usually is hard to construct. In 2004, Korobeinikov used the Volterra-type Lyapunov function to prove the global stability of the equilibrium states of a basic viral dynamic model, [18]. This function has been extensively used to prove the global stability of the equilibrium of infectious disease models, [19,20,31]. Vargas-De-León used the combinations of common quadratic, composite quadratic and Volterra-type functions to prove the global stability of equilibrium states of several epidemic models, [41], and for a hepatitis B model, with noncytolytic loss of infected cells, [42].

Another powerful tool to address the problem is the geometric method due to Li and Muldowney, which emerged from some papers in the middle of the nineties, [23–25]. Their approach is a generalization of Bendixson's criterion to systems of any finite dimensions and uses compound matrices. This method is nowadays classic, due to the wide range of applications, especially to mathematical models of biological interest. The majority of applications refer to epidemic models (see, e.g., [4, 7,10,21,24,26,39,43]) although applications to other population dynamics context may be also found, [6,8]. In [9] it has been shown that the mathematical structure of SEIR-like systems, whose analysis may generally be reduced to three-dimensional systems, appears to be particularly suitable for the applications of the method. On the other hand, applications to four-dimensional systems are not very common in the literature, because the procedure becomes particularly involved when $n \geq 4$. Examples are given by Ballyk and coworkers, [5], who applied the compound matrix techniques to a four-dimensional population model with peculiar symmetries, and Gumel and coworkers, [16], who studied a SVEIR (susceptible, vaccinated, exposed, infectious and recovered) model of severe acute respiratory syndrome (SARS) epidemic spread.

In this paper we will use both, the Lyapunov direct method and the geometric approach, to deal with the nonlinear stability of the infected equilibrium (i.e. equilibrium with all positive components) of the model for the viral dynamics of HIV-1 introduced in [37]. In particular, as it was recently shown for a tuberculosis model, [11], the geometric method will be applied by following the procedure given in [16]. We obtain sufficient conditions for the global stability, written in terms of the parameter of the system. Moreover, Lyapunov function will also be used to prove that the virus-free equilibrium is globally asymptotically stable when the basic reproduction number is less than one. Some numerical simulations are also performed to give a more complete representation of the system dynamics.

The paper is organized as follows: in Section 2 the model is introduced and some basic properties presented. The global asymptotic stability of the virus-free equilibrium is described in Section 3. In Section 4, the Lyapunov method is applied to study the global stability of the infected equilibrium. In Section 5, the global dynamics is studied by means of the Li–Muldowney geometric approach. Conclusions are given in Section 6.

2. The model and its basic properties

In 2007, Rong and coworkers, [37], introduced a stage-structured model for HIV-1 infection. The model includes a class of infected cells that are not yet producing virus, i.e. cells in the *eclipse phase*. This aspect makes the model an extension of basic HIV models, where the state variables are uninfected CD4⁺T cells, productively infected T cells, and free virus [33,34]. As a result, the model under consideration is a four-dimensional system of nonlinear ordinary differential equations. The rates of change of the state variables in each stage are represented by the following equations:

$$\begin{aligned}\dot{x} &= \lambda - \beta x(t)v(t) - \mu x(t) + \delta w(t), \\ \dot{y} &= \phi w(t) - \alpha y(t), \\ \dot{w} &= \beta x(t)v(t) - (\delta + \eta + \phi)w(t), \\ \dot{v} &= \sigma y(t) - \gamma v(t),\end{aligned}\tag{1}$$

where the upperdot denotes the time derivative, $d \cdot /dt$. In (1), the state variables $x(t)$, $y(t)$, $w(t)$ and $v(t)$ represent the concentration of uninfected CD4⁺T cells, productively infected cells, infected cells in the eclipse stage and free virus, at time t , respectively. To explain the parameters, we note that λ is the recruitment rate of uninfected CD4⁺T cells, and μ is the natural death rate of CD4⁺T cells. The term $\beta x(t)v(t)$ describes the incidence of HIV infection of health CD4⁺T cells, where β is the infection rate. Parameter ϕ is the rate at which infected cells in the eclipse stage become productively infected cells and these cells die at a rate η . The cells in the eclipse stage are already infected and may be killed by immune cells or cytopathic effects [2]. Then it is reasonable to assume that the average life span of uninfected cells ($1/\mu$) should be greater than, or equal to, the lifespan of cells in the eclipse stage ($1/\eta$). Productively infected cells die at a rate α . Parameter σ is the rate of production of virions by infected cells and γ is the clearance rate of virus particles.

Parameter δ needs some comments. As well explained in [37], a proportion of infected cells in the eclipse stage can revert to the uninfected state before the viral genome is integrated into the genome of the lymphocyte. In model (1) δ is the rate at which the cells in the eclipse phase may revert to the uninfected class.

All the parameters described above are assumed to be positive and non-negative initial values are associated to system (1).

We remark that a model for viral infection similar to (1) in which the reversion of cells from infected in the eclipse stage to the uninfected state is neglected, has been proposed by Korobeinikov, [18], who analyzed the global stability of equilibrium states.

We begin the analysis of the basic properties by observing that the non-negative octant

$$\mathbb{R}_+^4 = \{(x, y, w, v) \in \mathbb{R}^4: x \geq 0, y \geq 0, w \geq 0, v \geq 0\}$$

is positively invariant with respect to (1). The following theorem provides the boundedness of the solutions of system (1).

Theorem 2.1. *All the solutions of system (1) are uniformly bounded in the compact subset $\Theta \subseteq \mathbb{R}_+^4$.*

Proof. Let $(x(t), y(t), w(t), v(t))$ be any solution with positive initial conditions. Adding the first three equations and using $C(t) = x(t) + y(t) + w(t)$, we obtain for the total cells population: $\dot{C} \leq \lambda - \psi C$, where $\psi = \min\{\alpha, \eta, \mu\}$. It follows that $\limsup_{t \rightarrow \infty} C \leq \frac{\lambda}{\psi}$. The last equation of (1) then leads to

$$\dot{v}(t) = \sigma y - \gamma v \leq \frac{\lambda \sigma}{\psi} - \gamma v,$$

by a standard comparison theorem, we can conclude that

$$\limsup_{t \rightarrow \infty} v \leq \frac{\lambda \sigma}{\gamma \psi}.$$

Hence all the solutions of (1) which initiate in \mathbb{R}_+^4 are eventually confined in the region:

$$\Theta = \left\{ (x, y, w, v) \in \mathbb{R}_+^4: 0 \leq x, y, w \leq \frac{\lambda}{\psi}, 0 \leq v \leq \frac{\lambda \sigma}{\gamma \psi} \right\}.$$

This completes the proof. \square

As a corollary, the region Θ will attract all solutions of (1) starting in Θ and it is also positively invariant with respect to system (1).

We begin the analysis of the equilibria by observing that system (1) admits the virus-free equilibrium $E^\circ = (\lambda/\mu, 0, 0, 0)$. Define now the *basic reproduction number* for the viral infection as

$$R_0 = \frac{\beta \lambda \sigma \phi}{\alpha \gamma \mu (\delta + \eta + \phi)}.$$

The basic reproduction number is formally defined as the average number of secondary infectious individuals (in our case, cells) resulting from an average infectious individual following their introduction into a totally susceptible population, [3,13,40]. For a viral infection, R_0 is defined as the average number of secondary infected cells that are produced by any one productively infected cell when placed into an environment of otherwise uninfected cells, [15].

Usually, a sufficient condition for the persistence of the infection in the host population is that $R_0 > 1$, and this condition is also necessary for a large number of epidemic models (the ones that does not exhibit the phenomenon of *backward bifurcation*, for which there may be an epidemic spread also for values of R_0 below the unity, see e.g. [4]). Hence, $R_0 = 1$ is often a threshold value between epidemic and disease eradication. This is the case of system (1), as we will show. For now, observe that if $R_0 > 1$, then there exists a unique infected equilibrium, i.e. an equilibrium with positive components: $E^*(x^*, y^*, w^*, v^*)$, where

$$x^* = \frac{\lambda}{\mu R_0}, \quad y^* = \frac{\phi}{\alpha} w^*, \quad w^* = \frac{\lambda}{\eta + \phi} \left(1 - \frac{1}{R_0}\right), \quad v^* = \frac{\sigma \phi}{\alpha \gamma} w^*. \quad (2)$$

3. Global dynamic of the virus-free equilibrium

In this section we show that if $R_0 \leq 1$, then the virus-free equilibrium is globally stable. Hence, all solutions initiating in \mathbb{R}_+^4 approach E° .

Theorem 3.1. *If $R_0 \leq 1$, then the virus-free equilibrium E° is globally asymptotically stable in \mathbb{R}_+^4 .*

Proof. Define the global Lyapunov function $W : \{(x, y, w, v) \in \mathbb{R}_+^4 : x > 0\} \rightarrow \mathbb{R}$ by

$$W(x, y, w, v) = \left(x - x^\circ - x^\circ \ln \frac{x}{x^\circ}\right) + \frac{\delta}{2(\mu + \eta + \phi)x^\circ} [(x - x^\circ) + w]^2 + \frac{(\delta + \eta + \phi)}{\phi} y + w + \frac{\alpha(\delta + \eta + \phi)}{\sigma\phi} v. \quad (3)$$

Then W is C^1 on the interior of \mathbb{R}_+^4 , E° is the global minimum of W on \mathbb{R}_+^4 , and $W(x^\circ, 0, 0, 0) = 0$, where $x^\circ = \lambda/\mu$. The derivative of (3) along the solution curves of (1) is given by the equation:

$$\frac{dW}{dt} = \frac{(x - x^\circ)}{x} \dot{x} + \frac{\delta}{(\mu + \eta + \phi)x^\circ} [(x - x^\circ) + w] (\dot{x} + \dot{w}) + \frac{(\delta + \eta + \phi)}{\phi} \dot{y} + \dot{w} + \frac{\alpha(\delta + \eta + \phi)}{\sigma\phi} \dot{v},$$

that is,

$$\begin{aligned} \frac{dW}{dt} &= \frac{(x - x^\circ)}{x} (\lambda - \mu x - \beta x v + \delta w) + \frac{\delta}{(\mu + \eta + \phi)x^\circ} [(x - x^\circ) + w] (\lambda - \mu x - (\eta + \phi)w) \\ &\quad + \frac{(\delta + \eta + \phi)}{\phi} (\phi w - \alpha y) + (\beta x v - (\delta + \eta + \phi)w) + \frac{\alpha(\delta + \eta + \phi)}{\sigma\phi} (\sigma y - \gamma v). \end{aligned}$$

Using $\lambda = \mu x^\circ$, we obtain:

$$\begin{aligned} \frac{dW}{dt} &= \frac{(x - x^\circ)}{x} (-\mu(x - x^\circ) - \beta x v + \delta w) + \frac{\delta}{(\mu + \eta + \phi)x^\circ} [(x - x^\circ) + w] (-\mu(x - x^\circ) - (\eta + \phi)w) \\ &\quad + \beta x v - \frac{\alpha\gamma(\delta + \eta + \phi)}{\sigma\phi} v. \end{aligned}$$

Notice that:

$$\delta w \frac{(x - x^\circ)}{x} = -\delta w \frac{(x - x^\circ)^2}{xx^\circ} + \frac{\delta}{x^\circ} (x - x^\circ). \quad (4)$$

Substituting (4) and simplifying, we get:

$$\frac{dW}{dt} = -\left(\mu x^\circ + \frac{\delta\mu}{(\eta + \mu + \phi)} x + \delta w\right) \frac{(x - x^\circ)^2}{xx^\circ} - \frac{\delta(\eta + \phi)w^2}{(\eta + \mu + \phi)x^\circ} - \frac{\alpha\gamma(\delta + \eta + \phi)}{\sigma\phi} \left(1 - \frac{\beta\sigma\phi x^\circ}{\alpha\gamma(\delta + \eta + \phi)}\right) v.$$

By rewriting dW/dt in terms of basic reproduction number, we have

$$\frac{dW}{dt} = -\left(\mu x^\circ + \frac{\delta\mu}{(\eta + \mu + \phi)} x + \delta w\right) \frac{(x - x^\circ)^2}{xx^\circ} - \frac{\delta(\eta + \phi)w^2}{(\eta + \mu + \phi)x^\circ} - \frac{\alpha\gamma(\delta + \eta + \phi)}{\sigma\phi} (1 - R_0) v.$$

Clearly, if $R_0 \leq 1$, we have that $dW/dt \leq 0$ for all $x, y, w, v > 0$. Thus, the virus-free equilibrium E° is stable. Furthermore, $dW/dt = 0$, when $x = x^\circ$ and $w = v = 0$. Let \mathbb{M} be the largest invariant set in the set

$$\mathbb{E} = \{(x, y, w, v) \in \mathbb{R}_+^4 : dW(x, y, w, v)/dt = 0\} = \{(x, y, w, v) \in \mathbb{R}_+^4 : x = x^\circ, y \geq 0, w = 0, v = 0\}.$$

We have from the fourth equation of (1) that $\mathbb{M} = \{E^\circ\}$. It follows from LaSalle's invariance principle that the virus-free equilibrium E° is globally asymptotically stable. \square

An immediate consequence is the following:

Corollary 1. If $R_0 \leq 1$, then the virus-free equilibrium E° of (1) is globally asymptotically stable in Θ .

4. Global stability of the infected equilibrium by means of Lyapunov functions

In this section, we use the Lyapunov direct method to establish sufficient conditions for the global asymptotic stability of the unique infected equilibrium E^* in $\text{int}(\mathbb{R}_+^4)$ when $R_0 > 1$.

Theorem 4.1. Let $R_0 > 1$. If

$$1 < R_0 \leq 1 + \frac{\eta + \phi}{\delta}, \quad (5)$$

then the unique infected equilibrium, E^* , of (1) is globally asymptotically stable in the interior of \mathbb{R}_+^4 .

Proof. Define the global Lyapunov function: $L : \{(x, y, w, v) \in \mathbb{R}_+^4 : x, y, w, v > 0\} \rightarrow \mathbb{R}$, such that:

$$L(x, w, y, v) = \left(x - x^* - x^* \ln \frac{x}{x^*}\right) + \frac{\beta x^* v^*}{\phi w^*} \left(y - y^* - y^* \ln \frac{y}{y^*}\right) + \frac{\delta}{2(\mu + \eta + \phi)x^*} [(x - x^*) + (w - w^*)]^2 \\ + \left(w - w^* - w^* \ln \frac{w}{w^*}\right) + \frac{\beta x^* v^*}{\sigma y^*} \left(v - v^* - v^* \ln \frac{v}{v^*}\right). \quad (6)$$

Then L is C^1 on the interior of \mathbb{R}_+^4 , E^* is the global minimum of L on \mathbb{R}_+^4 , and $L(x^*, y^*, w^*, v^*) = 0$. At infected equilibrium, we have:

$$\lambda = \mu x^* + \beta x^* v^* - \delta w^*, \quad (7)$$

$$\alpha = \phi \frac{w^*}{y^*}, \quad (8)$$

$$\lambda = \mu x^* + \alpha y^*, \quad (9)$$

$$(\delta + \eta + \phi) = \frac{\beta x^* v^*}{w^*}, \quad (10)$$

$$\gamma = \sigma \frac{y^*}{v^*}. \quad (11)$$

The derivative of (6) along the solution curves of (1) in \mathbb{R}_+^4 is given by the expression:

$$\frac{dL}{dt} = \left(1 - \frac{x^*}{x}\right) \dot{x} + \frac{\beta x^* v^*}{\phi w^*} \left(1 - \frac{y^*}{y}\right) \dot{y} + \frac{\delta}{(\mu + \eta + \phi)x^*} [(x - x^*) + (w - w^*)] (\dot{x} + \dot{w}) \\ + \left(1 - \frac{w^*}{w}\right) \dot{w} + \frac{\beta x^* v^*}{\sigma y^*} \left(1 - \frac{v^*}{v}\right) \dot{v} \\ = \left(1 - \frac{x^*}{x}\right) (\lambda - \mu x - \beta x v + \delta w) + \frac{\beta x^* v^*}{\phi w^*} \left(1 - \frac{y^*}{y}\right) (\phi w - \alpha y) \\ + \frac{\delta}{(\mu + \eta + \phi)x^*} [(x - x^*) + (w - w^*)] (\lambda - \mu x - (\eta + \phi)w) \\ + \left(1 - \frac{w^*}{w}\right) (\beta x v - (\delta + \eta + \phi)w) + \frac{\beta x^* v^*}{\sigma y^*} \left(1 - \frac{v^*}{v}\right) (\sigma y - \gamma v).$$

Using (7)–(11), we obtain:

$$\frac{dL}{dt} = \left(1 - \frac{x^*}{x}\right) (-\mu(x - x^*) - \beta x v + \beta x^* v^* + \delta(w - w^*)) + \frac{\beta x^* v^*}{\phi w^*} \left(1 - \frac{y^*}{y}\right) (\phi w - \phi w^* \frac{y}{y^*}) \\ + \frac{\delta}{(\mu + \eta + \phi)x^*} [(x - x^*) + (w - w^*)] (-\mu(x - x^*) - (\eta + \phi)(w - w^*)) \\ + \left(1 - \frac{w^*}{w}\right) (\beta x v - \beta x^* v^* \frac{w}{w^*}) + \frac{\beta x^* v^*}{\sigma y^*} \left(1 - \frac{v^*}{v}\right) (\sigma y - \sigma y^* \frac{v}{v^*}).$$

Notice that:

$$\delta \left(1 - \frac{x^*}{x}\right) (w - w^*) = -\delta(w - w^*) \frac{(x - x^*)^2}{x x^*} + \frac{\delta}{x^*} (x - x^*) (w - w^*).$$

Thus,

$$\frac{dL}{dt} = -(\mu x^* + \delta(w - w^*)) \frac{(x - x^*)^2}{x x^*} + \frac{\delta}{x^*} (x - x^*) (w - w^*) \\ + \beta x^* v^* \left(1 - \frac{x v}{x^* v^*} - \frac{x^*}{x} + \frac{v}{v^*}\right) + \beta x^* v^* \left(\frac{w}{w^*} - \frac{y}{y^*} - \frac{y^* w}{y w^*} + 1\right) \\ - \frac{\delta}{x^*} \left(\frac{\mu}{\mu + \eta + \phi} (x - x^*)^2 + (x - x^*) (w - w^*) + \frac{(\eta + \phi)}{\mu + \eta + \phi} (w - w^*)^2\right) \\ + \beta x^* v^* \left(\frac{x v}{x^* v^*} - \frac{w}{w^*} - \frac{x w^* v}{x^* w v^*} + 1\right) + \beta x^* v^* \left(\frac{y}{y^*} - \frac{v}{v^*} - \frac{y v^*}{y^* v} + 1\right).$$

After some algebraic manipulations, we obtain:

$$\begin{aligned} \frac{dL}{dt} = & - \left(\mu x^* - \delta w^* + \delta w + \frac{\mu \delta x}{\mu + \eta + \phi} \right) \frac{(x - x^*)^2}{xx^*} - \frac{\delta(\eta + \phi)}{(\mu + \eta + \phi)x^*} (w - w^*)^2 \\ & - \beta x^* v^* \left(\frac{x^*}{x} + \frac{yv^*}{y^*v} + \frac{wy^*}{w^*y} + \frac{xw^*v}{x^*wv^*} - 4 \right). \end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric mean, it follows that:

$$\frac{x^*}{x} + \frac{yv^*}{y^*v} + \frac{wy^*}{w^*y} + \frac{xw^*v}{x^*wv^*} - 4 \geq 0,$$

and the equality holds only for $x = x^*$, $y = y^*$, $w = w^*$ and $v = v^*$.

Therefore, if $\mu x^* - \delta w^* \geq 0$ then $dL/dt \leq 0$ holds for all $x, y, w, v > 0$. Thus, the infected equilibrium state E^* is stable and we have $dL/dt = 0$ if and only if $x = x^*$, $y = y^*$, $w = w^*$ and $v = v^*$ holds. The largest compact invariant set in $\{(x, y, w, v) \in \mathbb{R}_+^4 : dL/dt = 0\}$ is the singleton $\{E^*\}$. Therefore, the infected equilibrium E^* is globally asymptotically stable in the interior of \mathbb{R}_+^4 by LaSalle's invariance principle when $R_0 > 1$.

Finally, we show that the condition $\mu x^* - \delta w^* \geq 0$ is equivalent to the condition (5). Using x^* and w^* of (2), the inequality $\mu x^* - \delta w^* \geq 0$ may be written

$$\lambda \left[\frac{1}{R_0} \left(1 + \frac{\delta}{\eta + \phi} \right) - \frac{\delta}{\eta + \phi} \right] \geq 0,$$

so that

$$\frac{\delta \lambda}{(\eta + \phi) R_0} \left[\left(1 + \frac{\eta + \phi}{\delta} \right) - R_0 \right] \geq 0,$$

and

$$R_0 \leq 1 + \frac{\eta + \phi}{\delta}.$$

Hence the sufficient conditions, in terms of R_0 , can be written

$$1 < R_0 \leq 1 + \frac{\eta + \phi}{\delta},$$

and the proof is completed. \square

Remark 4.1. When $\delta = 0$, the model is simplified to the basic viral dynamics model with exposed period, [18].

5. Global stability of the infected equilibrium by means of the geometric approach

In this section, we will use the geometric approach to global stability, [22,23,25], in order to study the global stability of the infected equilibrium. We follow the approach used in [16] for a SVEIR model of SARS epidemic spread and employed also in [11] for a tuberculosis model.

Consider the autonomous dynamical system:

$$\dot{x} = f(x), \tag{12}$$

where $f : D \rightarrow \mathbf{R}^n$, $D \subset \mathbf{R}^n$ open set and simply connected and $f \in C^1(D)$. Let x^* be an equilibrium of (12), i.e. $f(x^*) = 0$. We recall that x^* is said to be *globally stable* in D if it is locally stable and all trajectories in D converge to x^* .

Let $Q(x)$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 on D and consider

$$A = Q_f Q^{-1} + Q M Q^{-1},$$

where the matrix Q_f is

$$(q_{ij}(x))_f = (\partial q_{ij}(x)/\partial x)^T \cdot f(x) = \nabla q_{ij} \cdot f(x),$$

and the matrix M is the second additive compound matrix of the Jacobian matrix J . Consider the Lozinskii measure $\bar{\mu}$ of A with respect to a vector norm $\|\cdot\|$ in $\mathbf{R}^{\binom{n}{2}}$, that is:

$$\bar{\mu}(A) = \lim_{h \rightarrow 0^+} \frac{\|I + hA\|}{h}.$$

We will apply the following [23]:

Theorem 5.1. (See [23].) If D_1 is a compact absorbing subset in the interior of D , and there exist $\zeta > 0$ and the Lozinskiĭ measure $\bar{\mu}(A) \leq -\zeta$ for all $x \in D_1$, then every omega limit point of system (1) in the interior of D is an equilibrium in D_1 .

In Section 2 the existence of equilibria has been discussed. If $R_0 > 1$, then there exists a unique infected equilibrium E^* . Furthermore, we know that $R_0 > 1$ implies that the virus-free equilibrium E° is unstable. The instability of E° , together with $E^\circ \in \partial\Theta$, imply the uniform persistence of the state variables, [14], i.e. there exists a constant $\epsilon > 0$ such that:

$$\liminf_{t \rightarrow \infty} x_i > \epsilon, \quad \text{for } x_i = x, y, w, v,$$

where the x_i 's indicate the state variables of system (1). The uniform persistence, together with boundedness of Θ , is equivalent to the existence of a compact set in the interior of Θ which is absorbing for (1), see [17]. Hence Theorem 5.1 may be applied, with $D = \Theta$.

We remark that the uniform persistence may be accomplished in a different way, using the Lyapunov-based approach proposed in [28]. A result similar to Corollary 1 in [28] may be obtained using the auxiliary function:

$$\zeta(t) = \frac{\phi(1 - \rho^*)}{(\delta + \eta + \phi)} w + y + \frac{\alpha}{\sigma} v,$$

where $\rho^* > 0$ is a sufficiently small constant.

According to [29], the Lozinskiĭ measure in Theorem 5.1 can be evaluated as:

$$\bar{\mu}(A) = \inf\{c: D_+ \|z\| \leq c \|z\|, \text{ for all solutions of } z' = Az\},$$

where D_+ is the right-hand derivative. When $R_0 > 1$ the infected equilibrium is locally stable. Hence, in order to apply Theorem 5.1 and get the global asymptotic stability, it is necessary to find a norm $\|\cdot\|$ such that $\bar{\mu}(A) < 0$ for all x in the interior of D .

The Jacobian matrix J of (1) is given by:

$$J = \begin{pmatrix} -\beta v - \mu & 0 & \delta & -\beta x \\ 0 & -\alpha & \phi & 0 \\ \beta v & 0 & -(\delta + \eta + \phi) & \beta x \\ 0 & \sigma & 0 & -\gamma \end{pmatrix}.$$

For a general 4×4 matrix,

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ a_{31} & a_{32} & a_{33} & a_{34} \\ a_{41} & a_{42} & a_{43} & a_{44} \end{pmatrix},$$

the second additive compound matrix is given by:

$$\begin{pmatrix} a_{11} + a_{22} & a_{23} & a_{24} & -a_{13} & -a_{14} & 0 \\ a_{32} & a_{11} + a_{33} & a_{34} & a_{12} & 0 & -a_{14} \\ a_{42} & a_{43} & a_{11} + a_{44} & 0 & a_{12} & a_{13} \\ -a_{31} & a_{21} & 0 & a_{22} + a_{33} & a_{34} & -a_{24} \\ -a_{41} & 0 & a_{21} & a_{43} & a_{22} + a_{44} & a_{23} \\ 0 & -a_{41} & a_{31} & -a_{42} & a_{32} & a_{33} + a_{44} \end{pmatrix}.$$

Hence, the second additive compound matrix of J is given by:

$$M = \begin{pmatrix} M_{11} & \phi & 0 & -\delta & \beta x & 0 \\ 0 & M_{22} & \beta x & 0 & 0 & \beta x \\ \sigma & 0 & M_{33} & 0 & 0 & \delta \\ -\beta v & 0 & 0 & M_{44} & \beta x & 0 \\ 0 & 0 & 0 & 0 & M_{55} & \phi \\ 0 & 0 & \beta v & -\sigma & 0 & M_{66} \end{pmatrix},$$

where

$$M_{11} = -\beta v - \mu - \alpha; \quad M_{22} = -\beta v - \mu - (\delta + \eta + \phi);$$

$$M_{33} = -\beta v - \mu - \gamma; \quad M_{44} = -\alpha - (\delta + \eta + \phi);$$

$$M_{55} = -\alpha - \gamma; \quad M_{66} = -(\delta + \eta + \phi) - \gamma.$$

Consider now the matrix Q , where:

$$q_{11} = q_{22} = q_{34} = 1/w; \quad q_{43} = q_{55} = q_{66} = 1/v$$

and all the other entries q_{ij} are zero.

Then we obtain the matrix $A = Q_f Q^{-1} + Q M Q^{-1}$, where Q_f is the derivative of Q in the direction of the vector field f . More precisely, we have:

$$Q_f Q^{-1} = -\text{diag}(\dot{w}/w, \dot{w}/w, \dot{w}/w, \dot{v}/v, \dot{v}/v, \dot{v}/v),$$

$$Q M Q^{-1} = \begin{pmatrix} M_{11} & \phi & -\delta & 0 & \beta \frac{xv}{w} & 0 \\ 0 & M_{22} & 0 & \beta \frac{xv}{w} & 0 & \beta \frac{xv}{w} \\ -\beta v & 0 & M_{44} & 0 & \beta \frac{xv}{w} & 0 \\ \sigma \frac{w}{v} & 0 & 0 & M_{33} & 0 & \delta \\ 0 & 0 & 0 & 0 & M_{55} & \phi \\ 0 & 0 & -\sigma \frac{w}{v} & \beta v & 0 & M_{66} \end{pmatrix}. \quad (13)$$

Hence, taking into account that,

$$\frac{\dot{w}}{w} = \beta \frac{xv}{w} - (\delta + \eta + \phi); \quad \frac{\dot{v}}{v} = \sigma \frac{y}{v} - \gamma,$$

we obtain the matrix A , where:

$$\begin{aligned} A_{11} &= -\beta v - \mu - \alpha - \beta \frac{xv}{w} + (\delta + \eta + \phi); & A_{22} &= -\beta v - \mu - \beta \frac{xv}{w}; \\ A_{33} &= -\alpha - \beta \frac{xv}{w}; & A_{44} &= -\beta v - \mu - \sigma \frac{y}{v}; \\ A_{55} &= -\alpha - \sigma \frac{y}{v}; & A_{66} &= -(\delta + \eta + \phi) - \sigma \frac{y}{v}, \end{aligned}$$

and all the other entries are as in the matrix (13).

Following [16], we consider the following norm on \mathbf{R}^6 :

$$\|\mathbf{z}\| = \max\{U_1, U_2\}, \quad (14)$$

where $\mathbf{z} \in \mathbf{R}^6$, with components z_i , $i = 1, \dots, 6$, and $U_1(z_1, z_2, z_3)$ is defined as:

$$\begin{cases} \max\{|z_1|, |z_2| + |z_3|\} & \text{if } \text{sgn}(z_1) = \text{sgn}(z_2) = \text{sgn}(z_3), \\ \max\{|z_2|, |z_1| + |z_3|\} & \text{if } \text{sgn}(z_1) = \text{sgn}(z_2) = -\text{sgn}(z_3), \\ \max\{|z_1|, |z_2|, |z_3|\} & \text{if } \text{sgn}(z_1) = -\text{sgn}(z_2) = \text{sgn}(z_3), \\ \max\{|z_1| + |z_3|, |z_2| + |z_3|\} & \text{if } -\text{sgn}(z_1) = \text{sgn}(z_2) = \text{sgn}(z_3) \end{cases}$$

and $U_2(z_4, z_5, z_6)$ is defined as:

$$\begin{cases} |z_4| + |z_5| + |z_6| & \text{if } \text{sgn}(z_4) = \text{sgn}(z_5) = \text{sgn}(z_6), \\ \max\{|z_4| + |z_5|, |z_4| + |z_6|\} & \text{if } \text{sgn}(z_4) = \text{sgn}(z_5) = -\text{sgn}(z_6), \\ \max\{|z_5|, |z_4| + |z_6|\} & \text{if } \text{sgn}(z_4) = -\text{sgn}(z_5) = \text{sgn}(z_6), \\ \max\{|z_4| + |z_6|, |z_5| + |z_6|\} & \text{if } -\text{sgn}(z_4) = \text{sgn}(z_5) = \text{sgn}(z_6). \end{cases}$$

We will use the following inequalities:

$$|z_1|, |z_2|, |z_3|, |z_2 + z_3| \leq U_1,$$

and

$$|z_i|, |z_i + z_j|, |z_4 + z_5 + z_6| \leq U_2(z); \quad i = 4, 5, 6; \quad i \neq j.$$

Set:

$$\theta = \frac{\lambda}{\psi \epsilon}$$

where ϵ is the constant of uniform persistence. We state the following theorem:

Theorem 5.2. For $R_0 > 1$, system (1) admits a unique infected equilibrium. It is globally asymptotically stable provided that

$$\eta + 2\phi + 2\delta < \mu < \alpha, \quad (15)$$

and

$$2\sigma\theta + \nu < \eta, \quad (16)$$

for some positive constant ν .

Proof. The proof is based on the estimate of the right derivative $D_+\|\mathbf{z}\|$ of the norm (14). This involves sixteen different cases according to the different orthants and the definition of the norm (14) within each orthant.

Case 1: $U_1 > U_2$, $z_1, z_2, z_3 > 0$, and $|z_1| > |z_2| + |z_3|$. Then:

$$\|\mathbf{z}\| = |z_1|, \quad (17)$$

so that

$$\begin{aligned} D_+\|\mathbf{z}\| &= z'_1 \\ &= A_{11}z_1 + A_{12}z_2 + A_{13}z_3 + A_{15}z_5 \\ &\leq \left[-\beta\nu - \mu - \alpha - \beta\frac{xv}{w} + (\delta + \eta + \phi) \right] |z_1| + \phi|z_2| - \delta|z_3| + \beta\frac{xv}{w}|z_5|. \end{aligned}$$

Using $|z_2| < |z_1|$, $-\delta|z_3| < 0$, $|z_5| < U_2 < |z_1|$, and (17), it follows:

$$D_+\|\mathbf{z}\| \leq [-(\mu + \alpha) + (\eta + \delta + 2\phi)]\|\mathbf{z}\|.$$

Taking into account of (15), we get

$$D_+\|\mathbf{z}\| \leq -\alpha\|\mathbf{z}\|.$$

Case 2: $U_1 > U_2$, $z_1, z_2, z_3 > 0$, and $|z_1| < |z_2| + |z_3|$. Then:

$$\|\mathbf{z}\| = |z_2| + |z_3|, \quad (18)$$

so that

$$\begin{aligned} D_+\|\mathbf{z}\| &= z'_2 + z'_3 \\ &= A_{31}z_1 + A_{22}z_2 + A_{23}z_3 + A_{24}z_4 + A_{35}z_5 + A_{26}z_6 \\ &\leq -\beta\nu|z_1| + \left(-\beta\nu - \mu - \beta\frac{xv}{w} \right) |z_2| - \left(\alpha + \beta\frac{xv}{w} \right) |z_3| + \beta\frac{xv}{w}|z_4 + z_5 + z_6|. \end{aligned}$$

Using now $|z_4 + z_5 + z_6| < U_2 < |z_2| + |z_3|$, $-\beta\nu(|z_1| + |z_2|) < 0$, and taking into account of and (18), we get:

$$D_+\|\mathbf{z}\| \leq -\min(\alpha, \mu)\|\mathbf{z}\|.$$

From (15):

$$D_+\|\mathbf{z}\| \leq -\mu\|\mathbf{z}\|.$$

The remaining fourteen cases are omitted for brevity (a complete analysis for a similar problem may be found in [12]). Their combination allow to obtain the following estimate:

$$D_+\|\mathbf{z}\| \leq -\nu\|\mathbf{z}\| \quad (19)$$

so that the global stability follows according to Theorem 5.1. \square

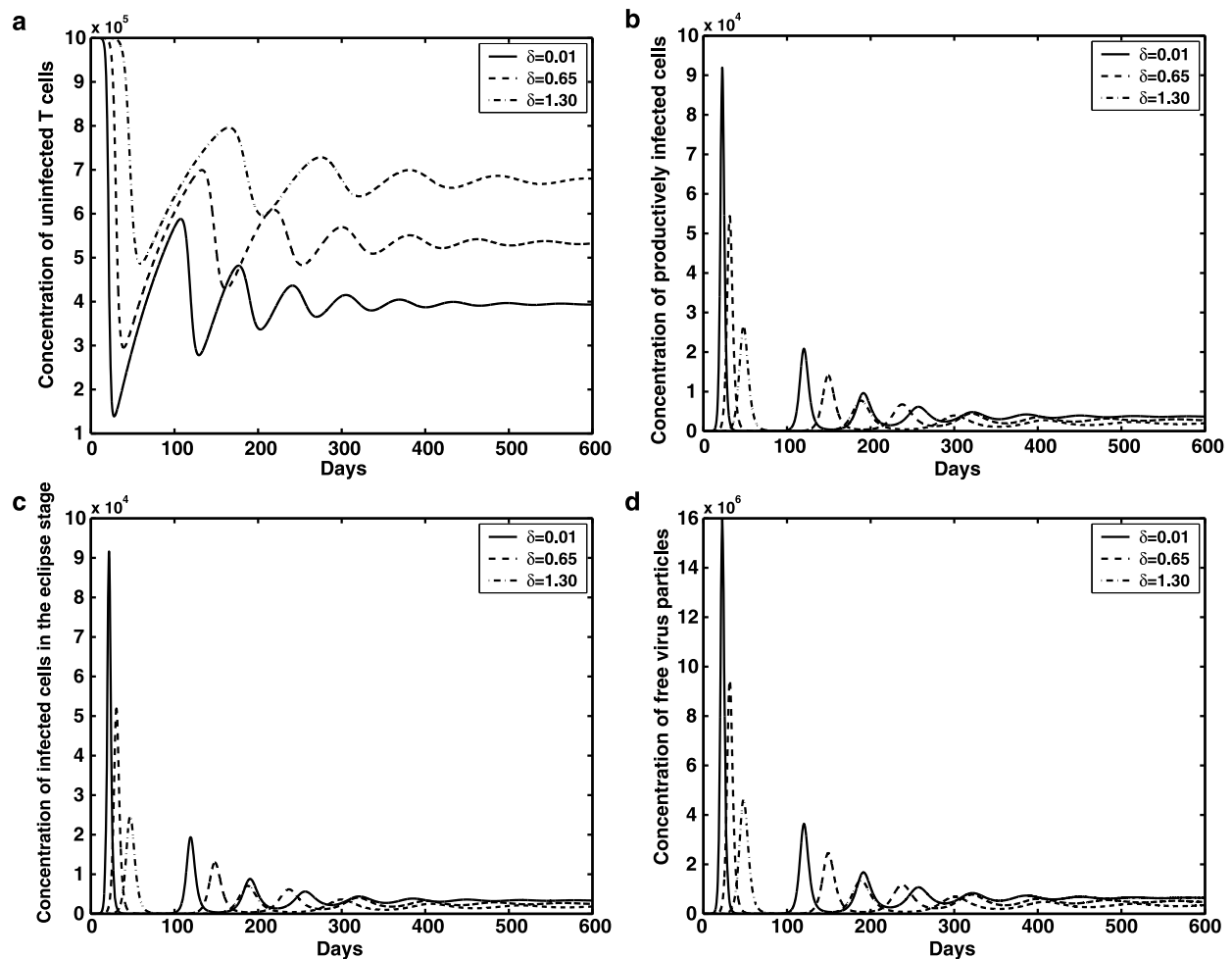


Fig. 1. Time plots for the virus dynamics of model (1) for different δ , and with $\phi = 1.1 \text{ d}^{-1}$ and $\eta = 0.7 \text{ d}^{-1}$. The other parameter values and initial conditions are as in [37]. That is: $\lambda = 10^4 \text{ ml}^{-1} \text{ d}^{-1}$; $1/\mu = 100 \text{ d}$; $\beta = 2.4 \cdot 10^{-8} \text{ ml d}^{-1}$; $1/\alpha = 1 \text{ d}$; $\sigma = 4000 \text{ d}^{-1}$; $\gamma = 23 \text{ d}^{-1}$; $x(0) = 10^6 \text{ ml}^{-1}$, $y(0) = 0$, $w(0) = 0$, $v(0) = 10^2 \text{ ml}^{-1}$. In this case $R_0 > 1$ and (5) is satisfied.

6. Conclusions

In this paper we have obtained two main results. Firstly, we have studied the global stability analysis for the model of HIV-1 infection recently introduced by Rong and coworkers, [37]. We have obtained sufficient conditions for the global asymptotic stability of both the virus-free and the infected equilibrium. Such aspect is worth to be carefully investigated because it is biologically relevant. For example, the global stability of the infected equilibrium gives the conditions, written in terms of the parameters of the system, under which the virus cannot be eliminated. We obtain our result in two different ways: using the Lyapunov direct method and the geometric method for global stability introduced by Li and Muldowney.

Secondly, our result is in some sense a *test* for the application of the two adopted methods. In fact, the four-dimensional nature of the model makes the use of the two nonlinear stability methods nontrivial. In particular, the applications of the geometric method becomes quite involved, and this explains why there are only few examples of such application in the literature for n -dimensional models, with $n \geq 4$.

Following the strategy of constructing a suitable norm on \mathbb{R}^6 , described into details in [30] and developed in [16] for a SVEIR model of SARS epidemic spread, we have obtained the sufficient conditions for the global stability of the infected equilibrium (Theorem 5.2). Such conditions involve the constant of uniform persistence, which may be not easily estimated.

More *quantitative* conditions, which are entirely written in terms of the parameters of the system, may be obtained by employing the Lyapunov direct method. We have built a Lyapunov function by combining linear, composite quadratic and Volterra-type functionals. In this way we are able to prove that the virus free-equilibrium is globally asymptotically stable when $R_0 \leq 1$ (Theorem 3.1) and that the infected equilibrium is globally asymptotically stable provided that the inequality (5) holds.

We are sure that the range of parameter values ensuring the global stability of the infected equilibria is larger than that indicated by our conditions. Indeed we have performed some numerical simulations which suggest that the infected

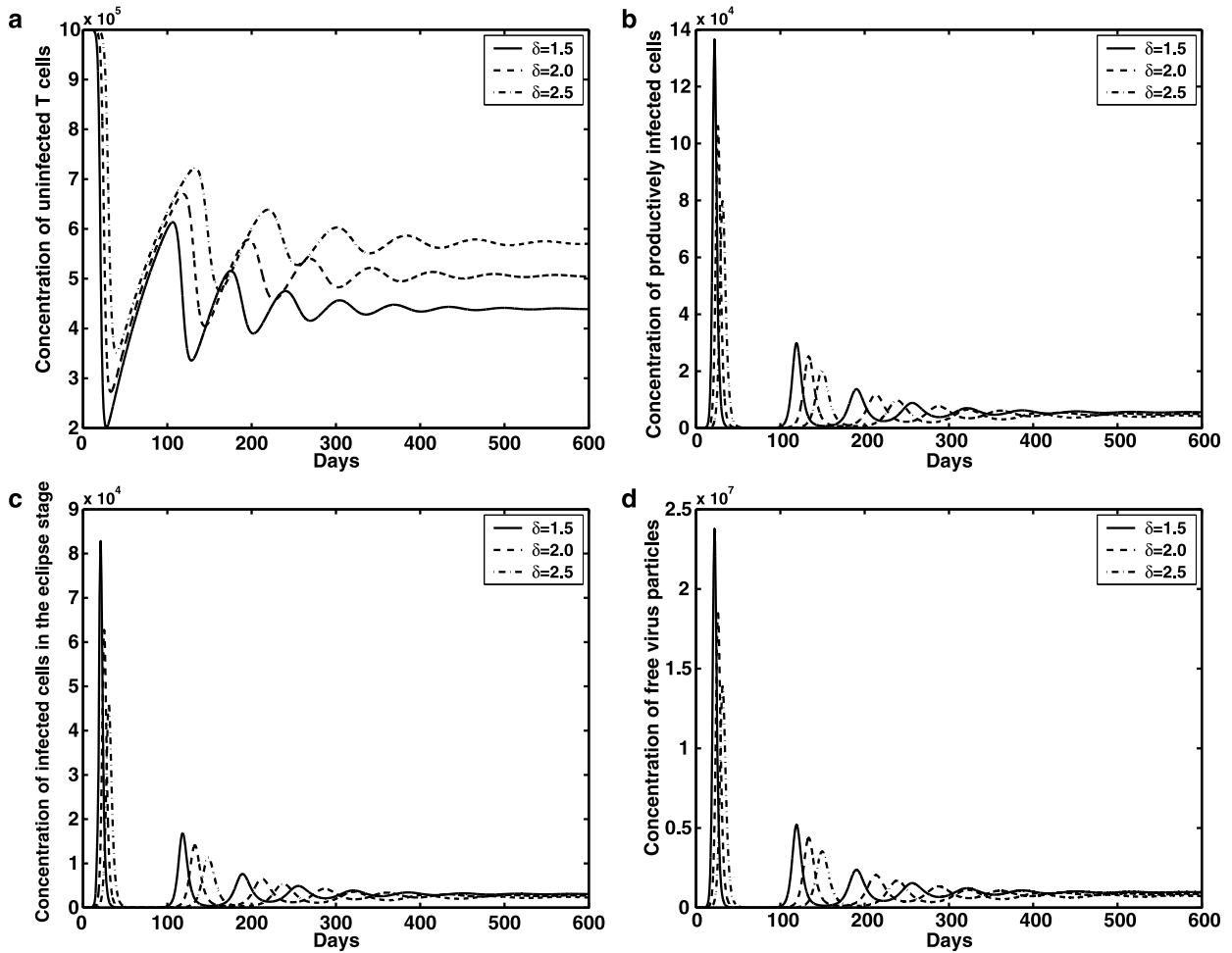


Fig. 2. Time plots for the virus dynamics of model (1) for different δ , and with $\phi = 1.81 \text{ d}^{-1}$ and $\eta = 0.011 \text{ d}^{-1}$. The other parameter values and initial conditions are as in [37]. That is: $\lambda = 10^4 \text{ ml}^{-1} \text{ d}^{-1}$; $1/\mu = 100 \text{ d}$; $\beta = 2.4 \cdot 10^{-8} \text{ ml d}^{-1}$; $1/\alpha = 1 \text{ d}$; $\sigma = 4000 \text{ d}^{-1}$; $\gamma = 23 \text{ d}^{-1}$; $x(0) = 10^6 \text{ ml}^{-1}$, $y(0) = 0$, $w(0) = 0$, $v(0) = 10^2 \text{ ml}^{-1}$. In this case $R_0 > 1$ and (5) are not satisfied.

equilibrium for the HIV-1 infection model, when exists, might always be globally asymptotically stable. Some of these simulations are shown in Figs. 1 and 2.

As a consequence, the inequality (5) could be relaxed to $R_0 > 1$. However, under some biological circumstances the right-hand side of inequality (5) may be very large. In particular, when the rate of reversion to the uninfected state δ is sufficiently small compared to the reciprocal of the average residence time in the infected stage in the eclipse state, $1/(\delta + \eta + \phi)$.

As for the sufficient conditions (15) and (16), we note that (15) is satisfied if the average life span of productively infected cells, $1/\alpha$, is less than the average life span of uninfected cells, $1/\mu$; and the average life span of uninfected cells is less than the average residence time in the infected stage in the eclipse state, $1/(\delta + \eta + \phi)$.

For η sufficiently large (i.e., a sufficiently short average life span of cells in the eclipse state), inequality (16) holds and the conclusion of Theorem 5.2 holds.

As a final remark, we underline that the sufficient conditions here obtained may be, in principle, improved. For example, the geometric approach to stability is based on two crucial choices: the entries of the matrix Q and the vector norm (14). Different choices of the matrix Q and of the vector norm could lead to better sufficient conditions than those found here, in the sense that the restrictions on the parameters may be weakened.

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